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December 23, 2019

Hon. William H. Pauley III
Daniel Patrick Moynihan
United States Courthouse
500 Pearl Street
New York, NY 10007

Re: Gayle, et al. v. Pfizer, et al., 1:19-CV-03451

Your Honor,

During the hearing of December 13, 2019, Your Honor asked Plaintiff for cases where courts had found that adverse event reports alone constituted new information. The following is Plaintiffs' response to the request, provided in letter form, as directed by the Court.

The Court need look no further than the Supreme Court decision in *Wyeth v. Levine*, 555 U.S. 555 (2009) to find that (1) the Supreme Court allowed plaintiff's claims, finding that adverse event reports constitute new information, and (2) the FDA itself found adverse event reports alone constituted new information when requiring the promethazine (Phenergan) label be changed.

In the decision, the Supreme Court wrote:

> We need not decide whether the 2008 CBE regulation is consistent with the FDCA and the previous version of the regulation, as Wyeth and the United States urge, because Wyeth could have revised Phenergan's label even in accordance with the amended regulation. As the FDA explained in its notice of the final rule, "'newly acquired information'" is not limited to new data, but also encompasses "new analyses of previously submitted data." *Id.*, at 49604. The rule accounts for the fact that risk information accumulates over time and that the same data may take on a different meaning in light of subsequent developments: "[I]f the sponsor submits adverse event information to FDA, and then later conducts a new analysis of data showing risks of a different type or of greater severity or frequency than did reports previously submitted to FDA, the sponsor meets the requirement for 'newly acquired information.'" *Id.*, at 49607; see also *id.*, at 49606.

> The record is limited concerning what **newly acquired information Wyeth had or *should have* had** about the risks of IV-push administration of Phenergan because Wyeth did not argue before the trial court that such information was required for a CBE labeling change. **Levine did, however, present evidence of at least 20 incidents prior to her injury in which a Phenergan injection resulted in gangrene and an amputation.** See App. 74, 252. After the first such incident came to Wyeth's attention in 1967, it notified the FDA and worked with the agency to change Phenergan's label. **In later years, as amputations continued to occur, Wyeth *could have* analyzed the accumulating data and added a stronger warning about IV-push administration of the drug.**

Wyeth v. Levine, 555 U.S. 555, 569-70 (2009) (Emphasis added).

From *Levine*, it is clear that (1) 20 adverse event reports that had already been submitted to the FDA was adequate to avoid preemption, (2) the relevant question is information that Wyeth had or ***should*** have had, and (3) the Supreme Court recognized that Wyeth could have analyzed the accumulating data and changed the label. These are precisely the issues before this Court in this case. After the Lipitor labeling change, there are thousands of reports of diabetes. Diabetes, to this day, is not included in the label. Plaintiffs have argued that there is a duty of pharmacovigilance to analyze the data, and that Defendants did not do so. Lastly, that new information that Pfizer had or ***should*** have had would have formed the basis of a labeling change.

To further reinforce the point, Plaintiffs' Counsel Keith Altman drafted a portion of one of the amici briefs filed in *Levine.*[1] *See* Exhibit A, Section I.C "Adverse Event Reports in the FDA Database." In that section, an analysis of adverse event reports ***already in the possession of the FDA*** was conducted. The results showed strong signals concerning the relationship between promethazine and amputations.

Following the ruling in *Levine*, Altman, a member of the International Society for Pharmacoepidemiology, expanded upon the *Levine* analysis and presented a scientific poster and the annual congress in August 2009. *See* Exhibit B. At the conference, several FDA officials conferred with Altman concerning the poster and took copies of the findings. Approximately three weeks later, on September 16, 2009, the FDA reached out to all manufacturers of promethazine (the generic version of Phenergan) concerning the risks of gangrene and amputations. *See* Exhibit C, physical pp. 23 of 41.[2] There, the FDA wrote that adverse event reports ***alone*** constituted new information:

> Since Promethazine Hydrochloride Injection, USP was approved on August 22, 2002, we have become aware of adverse event reports of severe tissue injury, including gangrene, with the use of Promethazine Hydrochloride Injection. We consider this

[1] Because Altman had not yet been sworn in as a member of the California bar, Altman's name could not appear on the briefing.

[2] Exhibit C is the labeling approval package for one of the generic versions of promethazine. Starting on page 23 of the 41-page package is the letter from the FDA concerning the findings on promethazine.

> information to be "new safety information" as defined in the Food and Drug Administration Amendments Act (FDAAA).

Looking to the promethazine experience as a whole, the Supreme Court found that 20 adverse event reports were adequate to change the label, which implicitly constituted new information that Wyeth could have analyzed the information and executed a Changes Being Effected. Furthermore, an analysis of the publicly available data showed that there was a clear signal of an increased risk and that the FDA itself called the analysis of the 20 or so adverse event reports new information. Combined with the duty to analyze adverse event information under 21 C.F.R. 314.80(b) and (c), the promethazine experience demonstrates that adverse event reports alone can be sufficient to constitute new information.

As to the instant case, Plaintiffs' proposed amended complaint is replete with references to Defendants' failure to warn for diabetes and failure to conduct proper pharmacovigilance. *See* ECF # 27-1, ¶¶ 48-52, 75-76, 87-96, and 123-130. More specifically, Defendants admit that diabetes is an unexpected adverse event with respect to the U.S. package insert because they submit these reports to the FDA as unexpected events. Thus, Defendants cannot possibly argue that thousands of reports of an unexpected event do not constitute new information.

Furthermore, Plaintiffs point out that Defendants were not only required to report the adverse events, but were required to analyze the adverse events. *Id.* ¶¶ 89-90, 123-130. In parallel with *Levine*, "[i]n later years, as [diabetes reports] continued to occur, [Pfizer] could have analyzed the accumulating data and added a [warning about diabetes]." Thus, *Levine*'s precedent supports the proposition that liability can attach because of Pfizer's failure to properly analyze the data.

Lastly, Plaintiffs allege that Defendants failed to seek to change the label to add diabetes. *Id.* ¶¶ 50-51. Plaintiffs also allege that the information warranted a change: "Had Defendants properly conducted pharmacovigilance as required, the totality of the information available, much of which was in the exclusive possession of Defendants, would have shown that the risks of diabetes through the use of LIPITOR® warranted the inclusion of a warning in the package insert." *Id*. ¶ 130

Defendants' reliance on *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019) is misplaced, as the cases are easily distinguished. *Gibbons* concerned an event that was already in the package insert. Here, we are dealing with an event that is unlabeled, and therefore, the influx of a large number of reports for an event that is unlabeled to this day clearly put Defendants on notice that the label was inadequate. As discussed above, Plaintiffs have alleged that Defendants were required to analyze the adverse events and failed to do so. The Supreme Court has recognized that in similar circumstances, the adverse event reports alone constitute new information, and combined with the ability of the manufacturer to analyze the data, allow for liability to attach. Thus, *Gibbons* does not support Defendants in this case.

In conclusion, under the guidance of the Supreme Court, given that diabetes is an unlabeled event, the influx of large numbers of adverse event reports (thousands) is more than sufficient to constitute new information. Furthermore, the duty to analyze such information can form the basis

of liability. Clearly, the Supreme Court recognized that a manufacturer should not be able to escape liability by not analyzing data as required by the FDA through the C.F.R. If so, then this would encourage manufacturers to fail to meet their obligations so as to insulate themselves from liability. This Court should not reward manufacturers, such as Pfizer, for "sticking their heads in the sand." It is clear that at this stage of the litigation, Plaintiffs have more than sufficiently alleged the existence of new information, and that Pfizer failed to act upon the new information. Defendants' motion should be denied.

Dated: December 23, 2019

Respectfully Submitted,

/s/ Keith Altman
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